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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/980,080	06/20/2003	Herve Jouishomme	PGI-1	5350

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 01/23/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/980,080	JOUISHOMME ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-94* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-94* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/27/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' election with traverse of the Group II claims, drawn to a method for screening for an anti-tumor substance, in the reply filed on 10/27/2005 is acknowledged. The traversal is on the ground(s) that the unifying concept is a mammalian tissue model comprising cells of at least two types in predetermined initial amounts and in 3D structure. This is not found persuasive because the unity of inventions is broken when a "special technical feature " (that defines a contribution which each of the claimed inventions, considered as a whole, makes over the prior art) is known in the prior art. In the instant case, a mammalian tissue model comprising cells of at least two types in predetermined initial amounts and in 3D structure is clearly known in the prior art. The requirement is still deemed proper and is therefore made final. Applicants' arguments are also moot in view of cancellation of all original claims including product claims drawn a mammalian tissue model. Thus, election of species and related arguments are moot.

New claims 56-94 as filed on 10/27/2005 are pending and under examination.

Claim Rejections - 35 USC § 112

Claims 63, 64, 71-76 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63 and 64 are indefinite because it is unclear what is "proliferation index" in the lack of definitions and because claim fails to point out what active steps are encompassed by the claimed phrase "proliferation is expressed as the proliferation index".

Claims 71 and 75 and recites "measuring modulation of apoptosis" but they fail to point out what active steps are encompassed by the claimed phrases.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 56, 57, 58, 62, 63, 71, 72, 75, 77, 79 and 94 are rejected under 35 U.S.C. 102(b) as being anticipated by Tofilon et al. ("Response to BCNU of spheroids grown from mixtures of drug-sensitive and drug- resistant cells". Cancer Chemother. Pharmacol. 1989. 20:89-95).

Claims are directed to a method for screening for an anti-tumor substance wherein the method comprises a) step of providing an in vitro model of a mammalian tissue model comprising cells of at least two types in predetermined initial amounts and arranged in 3D structure wherein cells of one first type are tumor cells; b) step of providing a candidate anti-tumor substance; c) step of culturing the cells in the presence and in the absence of the candidate substance; d) step of assessing characteristics of at least one type of cells in the presence and in the absence of the candidate substance and e) accepting or rejecting the candidate substance based on results of assessment. Some claims are further drawn to measuring proliferation of cells or modulation of apoptosis. Some claims are further drawn to the use of cells grown as spheroids in the absence of solid support.

The reference by Tofilon et al. discloses investigation of response to BCNU of spheroids grown from mixtures of drug-sensitive and drug- resistant tumor cells. The reference disclose method comprising active steps identical to the presently claimed method including a) step of providing an in vitro model of a mammalian or rat tissue model comprising cells of at least two

types such as drug sensitive cells and drug resistant cells wherein cells are combined in predetermined initial amounts; wherein cells are grown as spheroids or arranged in 3D structure and wherein cells are tumor cells and, thus, at least "first" cell type is tumor as required by the claimed invention; b) step of providing a candidate anti-tumor substance such as BCNU; c) step of culturing the cells in the presence and in the absence of the candidate substance BCNU (see Fig. 4 or table 2); d) step of assessing characteristics of at least one type of cells in the presence and in the absence of the candidate substance BCNU by measuring spheroids volume, cell survival and growth delay (Fig. 4 or table 2); e) accepting or rejecting the candidate substance based on results of assessment, for example: through evaluation of sensitivity or recovery of different type of spheroids (table 3). The mixed spheroids are dispersed to measure proliferation of cells (page 90, col. 2, par. 3-4). The reference demonstrates that mixed spheroids have different response to drug treatment depending on amounts of resistant and sensitive cells. Thus, the cited method encompasses measuring apoptosis modulation within the meaning of the claims. Therefore, the cited reference anticipates the claimed invention.

Claims 56, 57, 71, 75, 78, 83, 84, 88, 89 and 90 are rejected under 35 U.S.C. 102(b) as being anticipated by Sternlicht et al. ("The myoepithelial defense: a host defense against cancer". Medical Hypotheses. 1997. 48:37-46).

Claims are directed to a method for screening for an anti-tumor substance wherein the method comprises a) step of providing an in vitro model of a mammalian tissue model comprising cells of at least two types in predetermined initial amounts and arranged in 3D structure wherein cells of one first type are tumor cells; b) step of providing a candidate anti-

tumor substance; c) step of culturing the cells in the presence and in the absence of the candidate substance; d) step of assessing characteristics of at least one type of cells in the presence and in the absence of the candidate substance and e) accepting or rejecting the candidate substance based on results of assessment. Some claims are further drawn to measuring modulation of apoptosis or cell invasion. Some claims are further drawn to the use of cells grown on solid support.

The reference by Sternlicht et al. teaches the myoepithelial defense against cancer and discloses method comprising active steps identical to the presently claimed method, for example; page 44, col.1, par. 2 and Fig. 6. The cited method comprises a) step of providing an in vitro model of a mammalian or human tissue model comprising cells of two types human myoepithelial cells and malignant cells arranged in 3D structure on solid support (Fig. 6), wherein the cell amounts are monitored and, thus, cells are present in predetermined initial amounts within the meaning of the claims; b) step of providing a candidate anti-tumor substance or cycloheximide; c) step of culturing the cells in the presence and in the absence of the candidate substance (page 44, col. 1, par. 2, last 3 lines); d) step of assessing characteristics of cells such as invasive ability and e) assessing effects of cycloheximide and, thus, accepting or rejecting the candidate substance based on results of assessment within the meaning of the claimed invention. Therefore, the cited reference anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 56-94 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tofilon et al. and by Sternlicht et al. taken with Nygaard et al. (IDS reference), Tomasetto et al. (The Journal of Cell Biology. July 1993, Vol. 122, No. 1, pages 157-167) and US 5,518,915.

Claims are directed to a method for screening for an anti-tumor substance wherein the method comprises a) step of providing an in vitro model of a mammalian tissue model comprising cells of at least two types in predetermined initial amounts and arranged in 3D structure wherein cells of one first type are tumor cells; b) step of providing a candidate anti-tumor substance; c) step of culturing the cells in the presence and in the absence of the candidate substance; d) step of assessing characteristics of at least one type of cells in the presence and in the absence of the candidate substance and e) accepting or rejecting the candidate substance based on results of assessment. Some claims are further drawn to measuring of cell proliferation, measuring modulation of apoptosis or measuring gap junction intercellular communication (GJIC) with fluorescent dyes. Some claims are further drawn to the use of various mammalian cells grown in the absence of solid support or the absence of solid support.

The cited reference by Tofilon et al. and by Sternlicht et al. disclose the use of various mammalian tissue models for screening effects of test substances on cancer cells and their interactions wherein the tissue models comprise at least two types of cells including tumor cells and normal cells that are arranged in 3D structures with and without solid support. The cited methods include steps of measuring cell proliferation and modulation of apoptosis in the presence and in the absence of candidate or test substances. The cited references by Tofilon et al.

and by Sternlicht et al. are lacking particular disclosure related to additional protocols for evaluation of cell interactions in mixed populations involving fluorescent dyes and for evaluation of cell-cell communication in mixed populations through gap junction intercellular communication (GJIC) with fluorescent dye.

However, these protocols are known in the prior art and they have been suggested for evaluation of drug testing in 3D mammalian tissue models including evaluation of cancer therapy regiments. For example: Nygaard et al. teaches evaluation of brain tumor cell invasion in mixed co-cultures with normal brain cells by using differential cell staining with two different fluorescent dyes and suggests the model for evaluation of cancer therapy regiment (abstract and last lines of the reference). The reference by Tomasetto et al. teaches measuring GJIP by using fluorescent dye calcein in mixed populations of human tumor cells and normal epithelial cells and suggests the model for determining effects of drugs on role of GJIP in regulating or inhibiting tumor growth (abstract and last lines of the reference).

Although the cited reference by Tofilon et al. and by Sternlicht et al. might not explicitly disclose the use of all presently claimed cell types in mixed co-cultures, the cited US 5,518,915 teaches the use of various 3D mixed cell culture systems and it acknowledges benefits of 3D cell system over monolayer cell cultures particularly for evaluation of toxicity of anti-cancer test substances (entire document including col. 52, lines 35-40).

Therefore, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary. It would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the prior art methods for anti-tumor drug testing depending on a desired choice of particular mammalian cells to be tested.

The various protocols of assessing cell characteristics and cell-cell interactions/communications as claimed are obvious alternatives within the purview of ordinary skill in the art as adequately demonstrated by the cited prior art.

The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached at (571) 272-0926.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

AU 1651

January 19, 2006

VERA AFREMOVA

PRIMARY EXAMINER